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Research Article

Experience in a PHTS Expertise Centre: Yield of Thyroid Ultrasound Surveillance in Children with PTEN Hamartoma Tumor Syndrome

M.G. Bormans E et al. Thyroid Abnormalities in Children with PHTS

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What is already known on this topic?
Literature describes PHTS patients who developed thyroid abnormalities, including DTC, before the age of 18 years. However, the exact risk for DTC under age 18 is unknown and no consensus has been reached thus far about the age to initiate thyroid ultrasound surveillance in children with PTHS.

What this study adds?
This study provides unique data about thyroid surveillance in PHTS children. Our expertise centre agrees to start thyroid ultrasound surveillance in children, at least from age 12, in order to early detect DTC. To minimize unnecessary invasive fine needle aspirations and surgeries, surveillance should preferably be assigned to experienced clinicians.

ABSTRACT
Objective: Children with PTEN hamartoma tumor syndrome (PHTS) are at increased risk for developing thyroid abnormalities, including differentiated thyroid carcinoma (DTC). The Dutch PHTS guideline recommends ultrasound surveillance starting from age 18. Since the literature describes PHTS patients who developed DTC before age 18, the Dutch PHTS expertise centre has initiated annual ultrasound surveillance starting from age 12. The purpose of this study was to identify the yield of thyroid ultrasound surveillance in children.
Methods: A retrospective single centre cohort study was conducted. Pediatric PHTS patients who received thyroid ultrasound surveillance before age 18 between 2016–2023 were included. Patients' medical records have been reviewed. Primary outcomes included prevalence and time to develop thyroid nodules ≥10mm, nodular growth, goiter, thyroiditis and DTC. Descriptive statistics and Kaplan-Meier analyses were performed.
Results: Forty-three patients were included. Two patients (5%) were diagnosed with DTC at ages 12 and 17. Both DTCs were identified as minimally invasive follicular carcinoma at stages pT3NxMx and pT1NxMx respectively. A total of 84% were diagnosed with thyroid abnormalities at a median age of 12 years (range 9-18). Most common findings were benign, including nodular disease (74%), goiter (30%) and autoimmune thyroiditis (12%). Nodular growth was observed in 14 patients (33%) resulting in (hemi)thyroidectomy in 7 patients (16%).
Conclusion: Thyroid ultrasound surveillance resulted in the detection of DTC in 2/43 PHTS patients before age 18. These findings support the recommendation to initiate thyroid ultrasound surveillance in children at least from age 12, preferably within an expertise centre.
Keywords: PTEN Hamartoma Tumor Syndrome, thyroid ultrasound surveillance, differentiated thyroid carcinoma, thyroid nodules, goiter, children, Cowden syndrome

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INTRODUCTION
The PTEN Hamartoma Tumor Syndrome (PHTS) is a rare autosomal dominant hereditary syndrome caused by pathogenic variants in the phosphatase and tensin homolog gene (*PTEN*). *PTEN* is a tumor suppressor gene, that regulates cellular growth, migration and apoptosis (1). PHTS nowadays encompasses Cowden Syndrome, Bannayan-Riley-Ruvalcaba Syndrome and PTEN-related Proteus syndrome, previously thought to be distinct disorders. Clinical characteristics of PHTS in children include macrocephaly, developmental delay, autism or intellectual disability, hamartomas and cutaneous manifestations such as papillomatosis, lipomas, trichilemmomas and vascular malformations (2).
Patients with a *PTEN* variant are at increased risk for developing both benign and malignant tumors in variety of organs, most frequent in thyroid, breasts and endometrium. For thyroid cancer, the current Dutch PHTS guideline recommends annual palpation of the thyroid starting from PHTS diagnosis and ultrasound surveillance starting from the age of 18 years (3). The European PHTS guideline recommends ultrasound surveillance starting from the age of 18 years (4). However, differentiated thyroid carcinoma (DTC) can already develop in childhood (2, 4, 5). Previous studies have estimated the incidence of DTC in pediatric patients at 4-12% (2, 6, 7) and the median (range) age of DTC diagnosis in children is estimated at 12 years (4-17) (6). PHTS patients evaluated in the Radboud University Medical Centre (Radboudumc), the Dutch PHTS expertise centre, are offered annual thyroid ultrasound surveillance starting from the age of 12 since 2016. Yet, the evidence for this surveillance is limited, as little studies have been performed to evaluate thyroid surveillance outcomes in pediatric cohorts. Current surveillance guidelines are mostly based on expert opinion. Recommendations regarding the age to initiate thyroid surveillance range from age 7 to 18 years, or even at time of PHTS diagnosis and are not incorporated by current guidelines (5, 6, 8, 9). Moreover, pathology rates are likely overestimated due to ascertainment bias.

This study analyzed the value and clinical outcomes of thyroid ultrasound surveillance in the pediatric PHTS cohort of the Radboudumc starting from the age of 12. We aimed to provide recommendations regarding thyroid ultrasound surveillance in pediatric PHTS patients between age 12 to 18 years.

METHOD

Setting and Participants

We conducted a retrospective single centre cohort study including pediatric PHTS patients evaluated in the Radboudumc from 2016 till 2023. We retrospectively included all patients who were diagnosed with PHTS (clinically or genetically confirmed) and underwent thyroid ultrasound surveillance before the age of 18 years. A clinical diagnosis was based on a positive family history of PHTS in combination with clinical features. Genetical diagnosis was confirmed using either Sanger sequencing, in case of positive family history or high clinical suspicion, or whole exome sequencing, in case of a broader differential diagnosis. No minimal follow-up time was required. Ultrasounds were performed by specialized radiologists who use standardized protocols to assess thyroid surveillance ultrasounds. Our multidisciplinary expertise team included pediatric endocrinologists, a pediatric neurologist, clinical geneticists, nuclear radiologists and pathologists experienced in pediatric thyroid cancer, conform the Dutch recommendation guideline for the management of pediatric DTC (10). All patients gave informed consent to participate in this study. The research ethics committee of the Radboudumc (CMO Arnhem-Nijmegen) declared that ethical approval was not required for this retrospective study.

Data Collection

Patient data were obtained from the electronical medical records of the Radboudumc. For each patient, information regarding diagnosis, genetics, clinical characteristics, physical examination, laboratory values, ultrasound results and pathology reports were collected. Data up to and including age 18 were collected. Primary outcomes included the prevalence and time to develop thyroid nodules with size ≥10mm, nodular growth, goiter, thyroiditis and DTC. Nodular disease was defined as presence of any nodule, regardless of its size. Nodular growth was defined as growth that was clinically relevant according to the radiologist. This was considered by the radiologist in case of a 20% increase in ≥2 nodule dimensions and an enlargement of ≥2mm or a ≥50% increase in volume. (11) The WHO normative values for thyroid volume in children were used by the radiologists to define goiter. (12) Thyroiditis was defined as signs of thyroiditis visible on ultrasound according to the radiologist. Autoimmune thyroiditis was referred to as presence of autoantibodies in combination with signs of thyroiditis on ultrasound. The definition DTC was used when cancer of the thyroid was histologically proven. Secondary outcomes included physical examination findings, laboratory values, presence of nodules <10mm, presence of adenomas, fine needle aspiration (FNA) results, and treatment information. Treatment encompasses potassium iodide, hemithyroidectomy, cervical lymph node dissection and adjuvant I131. The Bethesda classification was used to describe FNA results. (13)

Statistical Analysis

Descriptive analyses were performed. Continuous data were presented as medians (range) or means (standard deviation). Categorical data were presented as absolute numbers and percentages. Kaplan-Meier analyses were performed to estimate the probability of developing thyroid ultrasound abnormalities over time. Right censoring was applied at last performed follow-up ultrasound or at the age of 18 years, whichever came first. Log-rank tests were performed to evaluate associations between patient characteristics and time-to-event of ultrasound abnormalities. *P*-values of <0.05 were considered as statistically significant. To correct for ascertainment bias, Kaplan-Meier analyses were performed without the index patients. Index patients were defined as patients who developed thyroid abnormalities prior to PHTS diagnosis. Statistical analyses were performed using IBM SPSS Statistics (V. 27.0).

RESULTS

Study Population and Clinical Characteristics

The medical files of all 142 pediatric PHTS patients known at the Radboudumc were screened for the presence of thyroid ultrasound reports. A total of 99 patients were excluded, mainly since they had not received thyroid ultrasound surveillance yet. (Figure 1) The final study cohort consisted of 43 patients: 27 males (63%) and 16 females (37%), including 3 sibling pairs. (Table 1) The median age at PHTS diagnosis was 5 years (1-14). In the majority of patients (79%), macrocephaly contributed to the PHTS diagnosis. Both mild and severe developmental delay were common clinical presenting features (65%). In 4 patients (9%) thyroid abnormalities led to PHTS diagnosis. During follow-up, macrocephaly was present in almost all patients (98%), with an average head circumference at standard deviation score (SDS) +3.9 (2.9-4.9). Subcutaneous lipomas were already present in 13 patients (30%). In a total of 14 patients (33%) a palpable mass was identified by physical examination of the thyroid gland; all of them had thyroid abnormalities (nodules≥10mm, goiter or thyroiditis) on their first ultrasound, although in one patient swelling was probably caused by an enlarged lymph node. A total of 20 patients (47%) had a family history of thyroid abnormalities (in both PHTS patients and healthy individuals), whereas 16 patients (36%) had no family history documented.

A *PTEN* variant was confirmed in 93% (40/43), while 7% (3/43) had a clinically confirmed PHTS diagnosis and a first-degree relative with PHTS. Details of the *PTEN* variant were available for 95% (38/40). Most variants (97%, 37/38) were categorized as (likely) pathogenic and a single variant (3%, 1/38) was categorized as variant of uncertain significance (VUS). In half of the patients PHTS inheritance was *de novo*.

Thyroid Ultrasound Findings

All patients received 1 or more ultrasound(s) during follow-up, with a median follow-up time between the first and last ultrasound of 2 years (0-7). Age at initial ultrasound varied between 2 and 16 years, with a median age of 12 years. The majority of patients received their initial ultrasound because of regular surveillance (79%, n=34), others due to a palpable thyroid mass (14%, n=6), because of parents' request (n=1), unexplained decline in development (n=1) or due to an early case of DTC in family history (n=1). Thyroid abnormalities were present on initial ultrasound in 72% (31/43), whereas 12% (5/43) developed abnormalities during follow-up. Ultrasound findings are presented in Table 2.

In total, 166 thyroid ultrasounds were performed in the pediatric cohort, with a median number of 3 (1-9) ultrasounds per individual. Eight cases (19%) received only 1 ultrasound, showing abnormalities (nodules <10 mm) in 4 of them.

Nodular disease was present in 74% (32/43). In 30 out of 32 patients (94%), this was multinodular disease. Nearly half of the patients (49%, n=21) developed a nodule ≥10mm. Figure 2 shows the time to diagnosis of nodular disease and nodular growth. Nodular growth was observed in 33% (14/43), leading to close monitoring in 8 patients (indicating that surveillance was repeated within 3, 6 or 9 months instead of annual). In 7 patients, nodular growth led to FNA performance.

Five patients (12%) had features of thyroiditis on ultrasound. All of them had presence of serum anti-thyroid peroxidase autoantibodies (anti-TPO), confirming diagnosis of autoimmune thyroiditis. In 3 of them, additional anti-thyroglobulin autoantibodies (anti-TG) were found. Goiter was diagnosed on ultrasound in 13 patients (30%). Figure 3 shows the cumulative risk for thyroiditis and goiter over time. Seven patients (16%) had a normal thyroid ultrasound. They all had a proven pathogenic *PTEN* variant. Five out of them were aged 12 (or younger) at the end of the study follow-up time.

Thyroid Abnormalities and Associations

Figure 2 shows that females in our cohort tended to develop nodules ≥10mm slightly earlier than males, although this was not significant (*P*=.237). Female sex led to significant earlier development of nodular growth (*P*=.008), goiter (*P*=.005) and thyroiditis (*P*=.027), shown in Figure 2 and 3. Moreover, patients with head circumference SDS >4.0 were significantly more likely to develop a nodule ≥10mm (*P*=.006) compared to patients with head circumference SDS ≤4.0. The cumulative risk of thyroid abnormalities was not significantly associated with

the presence of lipomas, family history of thyroid abnormalities or developmental delay as presenting clinical feature, as shown in Table 3. Results for Kaplan-Meier analyses excluding index patients were similar (data not shown).

Laboratory Results

Serum thyroid function was measured in 67% (29/43) of the patients. The majority (90%, 26/29) was euthyroid. Levothyroxine treatment was needed in 1 patient with hypothyroidism after total thyroidectomy. Anti-TPO was measured in 15 patients, whereas anti-TG was measured in 10 patients. Five patients had presence of serum thyroid autoantibodies.

Benign Thyroid Abnormalities Before 12 Years of Age

Before the age of 12, 9 patients received ultrasound surveillance. Eight of them already showed nodular thyroid abnormalities and 4 such cases underwent FNA and treatment (n=2) or close monitoring (n=2) before this age. The treatment performed before the age of 12 included a hemithyroidectomy in one case (resulted in follicular adenoma) and the start of potassium iodide in another case. All of the abnormalities found before the age of 12, were identified by a palpable thyroid mass and eventually resulted to be benign. The cumulative risk of abnormalities at age 12 was 30% for developing nodules ≥10mm, 8% for nodular growth, 23% for goiter, and 8% for thyroiditis. (Figure 2 and 3)

Cytology and Treatment

A total of 11 patients (26%) underwent one or more FNA(s), with 10 years being the youngest age of FNA performance. Six patients received multiple FNAs (up to a maximum of 4), mainly since their first cytology resulted in Bethesda 1 (13). Ultimately, in 2 patients cytology was classified as Bethesda 1, 4 patients had Bethesda category 2, 3 patients had Bethesda category 3 and 2 patients had Bethesda category 4 (13). A total of 9 patients (21%) needed treatment, at a median age of 13 years (11-17). Treatment included potassium iodide in 4 patients (9%). Six patients (14%) needed a hemithyroidectomy and 1 patient (2%) needed a total thyroidectomy. Prior to surgery, 6 out of 7 (86%) had a palpable thyroid mass.

Pathology Results

DTC was diagnosed in 2 patients (5%). One female patient was diagnosed with a minimally invasive follicular carcinoma of 5.6 cm (pT3NxMx) at age 12. She had a pathogenic *PTEN* variant and was known with multinodular goiter. After noticing a growing mass in her neck, clinicians identified this as a remarkably solid fast growing thyroid mass. Ultrasound imaging confirmed nodular growth with a volume that was doubled (from 6.1 ml to 12.8 ml) within 8 months. After 2 FNAs (Bethesda category 1 and 3), she underwent a hemithyroidectomy. Histopathology confirmed DTC whereafter a rest total thyroidectomy was performed with cervical lymph node dissection and adjunctive iodine-131. Another male patient was diagnosed with a minimally invasive follicular carcinoma of 1.5 cm (pT1NxMx) at age 17. PHTS diagnosis was clinically confirmed and he had a first-degree relative with a *PTEN* variant classified as VUS. No thyroid mass was found by physical examination. At age 15, ultrasound showed nodular growth and FNA resulted in Bethesda 2. After 2 years of close monitoring, the nodule volume almost doubled within 6 months (from 1.5 ml to 2.9 ml) and ultrasound imaging showed an irregular margin of the nodule. These ultrasound features, together with a low Technetium uptake on scintigraphy led to performance of a second FNA (Bethesda 4) and hemithyroidectomy thereafter. Given the small and low invasive character of this DTC, a favourable prognosis was predicted. Therefore, a total thyroidectomy and adjunctive iodine-131 were not performed, in shared decision with the patient.

In 2 out of 7 patients that underwent surgery, histopathology resulted to be malignant, while 5 had benign outcomes. (Table 2) All 5 patients with benign outcomes, had a palpable mass of the thyroid and multinodular disease.

DISCUSSION

Our study provides important and unique data about thyroid abnormalities in children diagnosed with PHTS, which can be used to establish surveillance guidelines for pediatric PHTS patients. Two patients (5%) in our pediatric PHTS cohort developed minimally invasive DTC at ages 12 and 17, which is a high and relevant rate when considering the short median follow-up period (2 years). The number of DTCs in our cohort is similar to the previously reported incidence rate of 4% to 12% for DTC in pediatric PHTS cohorts and these results are comparable to the yield of surveillance in adults from the same PHTS expertise centre. (2, 6, 7, 15). It is known that the DTC rate in PHTS children (older than age 10) is significantly higher compared to the general population. (16) The young age at DTC diagnosis in this study is in line with previous childhood diagnoses/reports, with the youngest reported case of DTC at 4 years of age (6, 17). Current available studies have recommended surveillance starting from the age of 10 (2, 4, 6), from the age of 7 (5, 18) or immediately after PHTS diagnosis (19, 20). The Pediatric Cancer Working Group of the American Association for Cancer Research (AACR) recommends to start surveillance when cancer incidence reaches ≥5% (21). Taken this together, clinicians in our expertise centre would recommend thyroid surveillance from at least the age of 12 years to detect DTC at an early stage and that even surveillance from age 10 could be considered.

The majority of thyroid abnormalities (94%, 34/36) identified by ultrasound were benign, including nodular disease, goiter, thyroiditis and follicular adenomas. These findings are in line with previously published studies in both adults and children. (2, 4, 15, 19, 22, 23). It is remarkable that 5 out of 7 patients who underwent (hemi)thyroidectomy had benign histopathology results, despite prior close ultrasound monitoring and/or FNA performance. These findings demonstrate that it is challenging to predict the presence of cancer based on ultrasound and/or FNA. The high prevalence of (growing) benign lesions in PHTS children poses a challenge for the interpretation of the ultrasound and FNA results, even for experienced clinicians. As a result, surgery with pathology examination is still required sometimes. Therefore, surveillance should preferably be performed within a centre experienced in PHTS or pediatric thyroid abnormalities in order to minimize the burden of (unnecessary) FNAs and proceed to surgery only in cases of high suspicion of a malignancy. Characteristics such as nodular growth, a palpable solid and growing mass or suspicious ultrasound findings (including irregular margins, hypoechogenicity, solid pattern, microcalcifications, intranodular vascularity and taller-than-wide shape) should lead to performance of FNA and further diagnostics (10). Treatment included the use of potassium iodide in a few patients (9%) with nodular growth. Potassium iodide is effective in reducing the volume of benign solitary thyroid nodules, however the effect on nodular growth in PHTS patients, is not known (14).

Clinical factors that might influence DTC diagnosis were studied. Females tend to develop nodules ≥10mm, nodular growth, goiter and thyroiditis at an earlier age than males. These results are consistent with previous observations in both the general population (24, 25) and pediatric PHTS cohorts (5). A possible explanation for this association is the growth-promoting effect of estrogen on nodular growth (26). Another association was found between head circumference SDS >4 and nodular disease, consistent with findings by Tuli et al. (4). Although further research is needed to confirm these associations in larger PHTS cohorts, these findings can lead to improvement of thyroid cancer surveillance programs (e.g. initiating surveillance earlier in females, patients with head circumference SDS >4 and possibly also in patients with other clinical features). It should be noted that the clinical PHTS phenotypes in children have not reached complete development yet.

It is worth noting that 6 out of 7 patients (86%) that underwent (hemi)thyroidectomy had a palpable mass of the thyroid prior to surgery. A palpable thyroid mass was also found in all patients (n=4) that required treatment or close monitoring before the age of 12 years. This suggests that they could have been identified by physical examination only. In one DTC case, thyroid palpation led to suspicion of a malignancy, while the other cancer patient had no palpable thyroid mass. It is known that palpation is not sensitive and therefore ultrasound surveillance cannot be replaced by palpation only (27). However, since palpation is a noninvasive and low-cost method which helped to diagnose DTC in one case, we agree with the recommendation of the Dutch PHTS guideline (2015) to palpate the thyroid annually starting from PHTS diagnosis (3).

Although 8 patients had laboratory abnormalities, only 1 patient needed levothyroxine therapy after undergoing a total thyroidectomy and the majority was euthyroid. Five out of 8 had thyroid autoantibodies additionally to signs of thyroiditis on ultrasound. This data suggests that measuring serum thyroid function or thyroid autoantibodies might only be useful post-operative or after discovering signs of thyroiditis on ultrasound. This is comparable to the findings of Smith et al., although, this needs to be confirmed in larger cohorts (5).
The most important advantage of surveillance in pediatric patients is the early detection of DTC in order to prevent advanced disease and decrease morbidity (28). In our cohort we detected DTC at an early stage and not advanced disease. Another advantage is the noninvasive and low-cost character of ultrasound surveillance. In our experience, it is parents' preference to start surveillance immediately after PHTS diagnosis. However, the most important disadvantage of ultrasound surveillance is the high risk of false-positive results and parents need to be counseled for that (27). Implementing thyroid ultrasound surveillance as standard care from age 10-12 onwards, will consequently lead to more (possibly unnecessary) invasive FNAs and surgeries, especially when performed by a less experienced clinician. Moreover, minimally invasive follicular thyroid carcinomas, as found in our cohort, are associated with low recurrence and/or metastases rates (29). Thus, although our surveillance led to diagnosis at an early stage, more research is needed to investigate the clinical benefit of earlier cancer detection. With our current knowledge, surveillance from age 10-12 onwards is justified and shared decision making is important to make considerations based on individual preferences.
Besides discussion about the time to initiate ultrasound surveillance, consensus about surveillance intervals has not been reached yet. While some studies recommend annual surveillance (2, 7, 30), others suggest prolonged surveillance intervals in specific cases (5, 6, 9, 15, 31). Our study could not provide recommendations about stratifying ultrasound surveillance intervals, since the collected data could not address this issue.

STUDY STRENGTHS AND LIMITATIONS

The major strength of this study is the relatively large cohort of pediatric PHTS patients who received regular follow-up within one hospital. As a worldwide recognized expertise centre in the care for PHTS patients, our institute has an experienced multidisciplinary team of clinicians. Due to the small size of our team, there is little chance of interobserver variation. Given the fact that PHTS is a rare disease, a retrospective study performed in an academic expertise centre, seemed to be most appropriate. Despite the retrospective design, surveillance outcomes were well-documented with limited missing data. In all PHTS studies, the reported numbers of thyroid pathology are probably overestimated, since (asymptomatic) unrecognized PHTS individuals are not evaluated in hospitals and therefore not included in studies. To minimize the effect of overestimation due to ascertainment bias, Kaplan-Meier analyses were performed without the 4 index patients (9%) that had thyroid pathology prior to PHTS diagnosis. All graphs were comparable to the ones including the index patients, suggesting that the effect of ascertainment bias might be moderate. One limitation is the effect of selection bias, since only 43 out of 142 patients had available ultrasound reports and were included in the study. It should be noted that not every participant reached the age of 18 at the end of this study. Furthermore, benign thyroid abnormalities were already present at initial ultrasound in the majority of patients (72%). As a result, our findings do not represent accurate incidence rates, as abnormalities might have been developed before the first surveillance moment. As the aim of surveillance is to identify DTC at an early stage, providing exact DTC numbers is more relevant. Left-censoring should be applied in larger cohorts to improve current incidence rates. In future research it would be useful to assess the risk of malignancy for each nodule, based on ultrasound images, according to the TI-RADS classification as performed by Driessen et al. (2023) (11, 15) .To be more conclusive about the yield of ultrasound surveillance, studying a larger cohort of pediatric patients would be ideal, preferably in a prospective design and during a longer follow-up period.

CONCLUSION

According to our study and the previous literature, thyroid ultrasound surveillance is useful from age 10-12 years onwards. PHTS children often have benign thyroid lesions, as part of their clinical phenotype. However, distinguishing these benign abnormalities from potential malignancies is challenging. A fast growing nodule and an atypical aspect of the nodule warrants suspicion and should lead to close monitoring or further invasive diagnostics, such as FNA. If diagnosis remains uncertain, hemithyroidectomy is required, which can still reveal a high percentage of benign histopathology results. In conclusion, thyroid surveillance is useful, however, given its complexity, it should preferably be performed in a centre with excellence in pediatric thyroid abnormalities or PHTS.

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Figure 1– Flowchart of the selection for inclusion in the study cohort

Figure 1 – Flowchart of the selection for inclusion in the study cohort

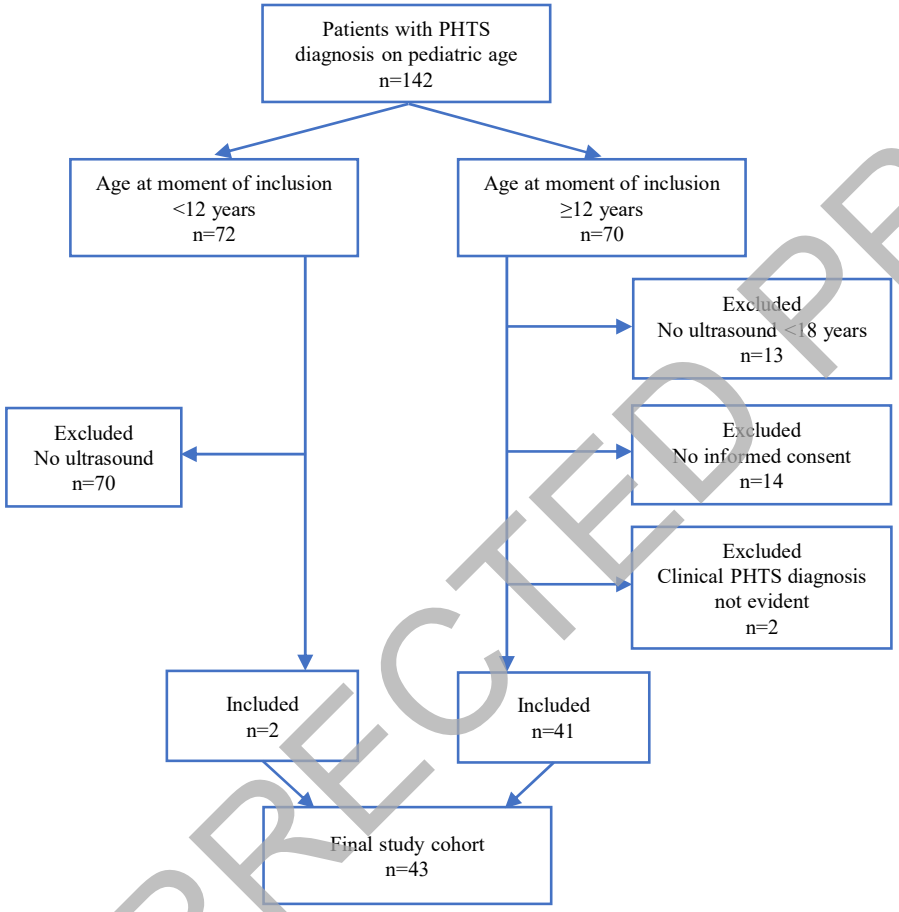


Table 1 – Characteristics of the pediatric PHTS study cohort (n=43)

Demographic	n (%) or median (range)
Sex	
Female	16 (37%)
Male	27 (63%)
Age PHTS diagnosis	5 (1-14)
Presenting clinical features	
Macrocephaly	34 (79%)
Developmental delay	28 (65%)
Autism and intellectual disability	5 (12%)
Family history of PHTS (at presentation)	9 (21%)
Thyroid pathology	4 (9%)
Skin lesions	8 (19%)
PHTS diagnosis	
Clinically confirmed	3 (7%)
Genetically confirmed	40 (93%)
Sanger sequencing	28 (70%)
Whole exome sequencing	9 (23%)
Unknown	3 (8%)
DNA tested on	
Blood	28 (70%)
Additional testing skin lesion	2 (5%)
Unknown	12 (30%)
***PTEN* variant**	
Pathogenic	34 (85%)
Likely pathogenic	3 (8%)
Variant of uncertain significance	1 (3%)
Unknown	2 (5%)
PHTS inheritance	
De novo	20 (50%)
Maternal	15 (38%)
Paternal	3 (8%)
Unknown	2 (5%)
Family history of thyroid pathology	
Yes	20 (47%)
No	7 (16%)
Unknown	16 (37%)

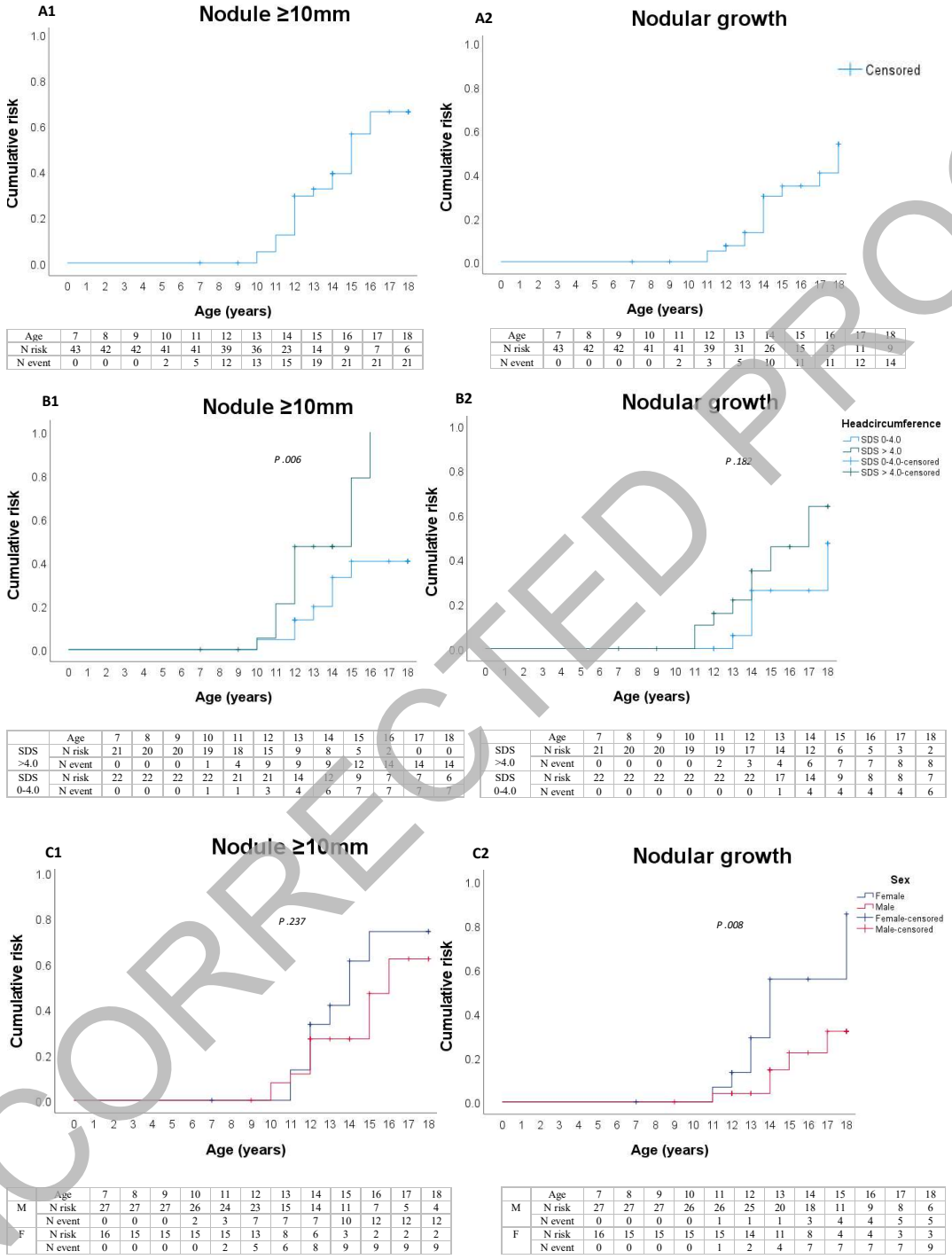
Table 2 – Thyroid Pathology findings in 43 pediatric PHTS patients

Thyroid Pathology	n=	%	Median age at diagnosis (range)
Physical examination			
Palpable mass thyroid	14	33	13 (9-16)
Ultrasound features			
Normal	7	16	Not applicable
All types of thyroid pathology	36	84	12 (9-18)
Nodule <5mm*	4	9	13 (9-14)
Nodule ≥5mm<10mm**	7	16	17 (13-18)
Nodule ≥10mm	21	74	12 (10-16)
Nodular growth	14	33	14 (11-18)
Thyroiditis	5	12	12 (11-14)
Goiter	13	30	12 (10-16)
Laboratory results			
Pathology in lab***	8	19	13 (11-17)
Benign pathology results			
Hyperplastic nodus	1	2	13
Follicular adenoma	3	7	14 (11-15)
Multinodular goiter	1	2	13
Lymphocytic thyroiditis	2	5	12 (11-13)
Malignant pathology results			
Minimal invasive follicular carcinoma	2	5	15 (12-17)

*Patients had nodule(s) of <5mm only.
**Patients had nodule(s) of ≥5mm<10mm only.
***Pathology in lab was defined as presence of thyroid autoantibodies or presence of thyroid dysfunction based on serum thyroid function tests.

Figure 2 – Cumulative risk of thyroid nodular disease
Time-to-event is presented for a nodule ≥10mm (1) and for nodular growth (2), for all patients (A), by head circumference SDS (B) and by sex (C) (M=male, F=female). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards. Log-rank tests P-values are provided.

Figure 2 – Cumulative risk of thyroid nodular disease



Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	43	42	42	41	41	39	36	23	14	9	7	6
N event	0	0	0	2	5	12	13	15	19	21	21	21

Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	43	42	42	41	41	39	31	26	15	13	11	9
N event	0	0	0	0	2	3	5	10	11	11	12	14

	Age	7	8	9	10	11	12	13	14	15	16	17	18
SDS >4.0	N risk	21	20	20	19	18	15	9	8	5	2	0	0
	N event	0	0	0	1	4	9	9	9	12	14	14	14
SDS 0-4.0	N risk	22	22	22	22	21	21	14	12	9	7	7	6
	N event	0	0	0	1	1	3	4	6	7	7	7	7

	Age	7	8	9	10	11	12	13	14	15	16	17	18
SDS >4.0	N risk	21	20	20	19	19	17	14	12	6	5	3	2
	N event	0	0	0	0	2	3	4	6	7	7	8	8
SDS 0-4.0	N risk	22	22	22	22	22	22	17	14	9	8	8	7
	N event	0	0	0	0	0	0	1	4	4	4	4	6

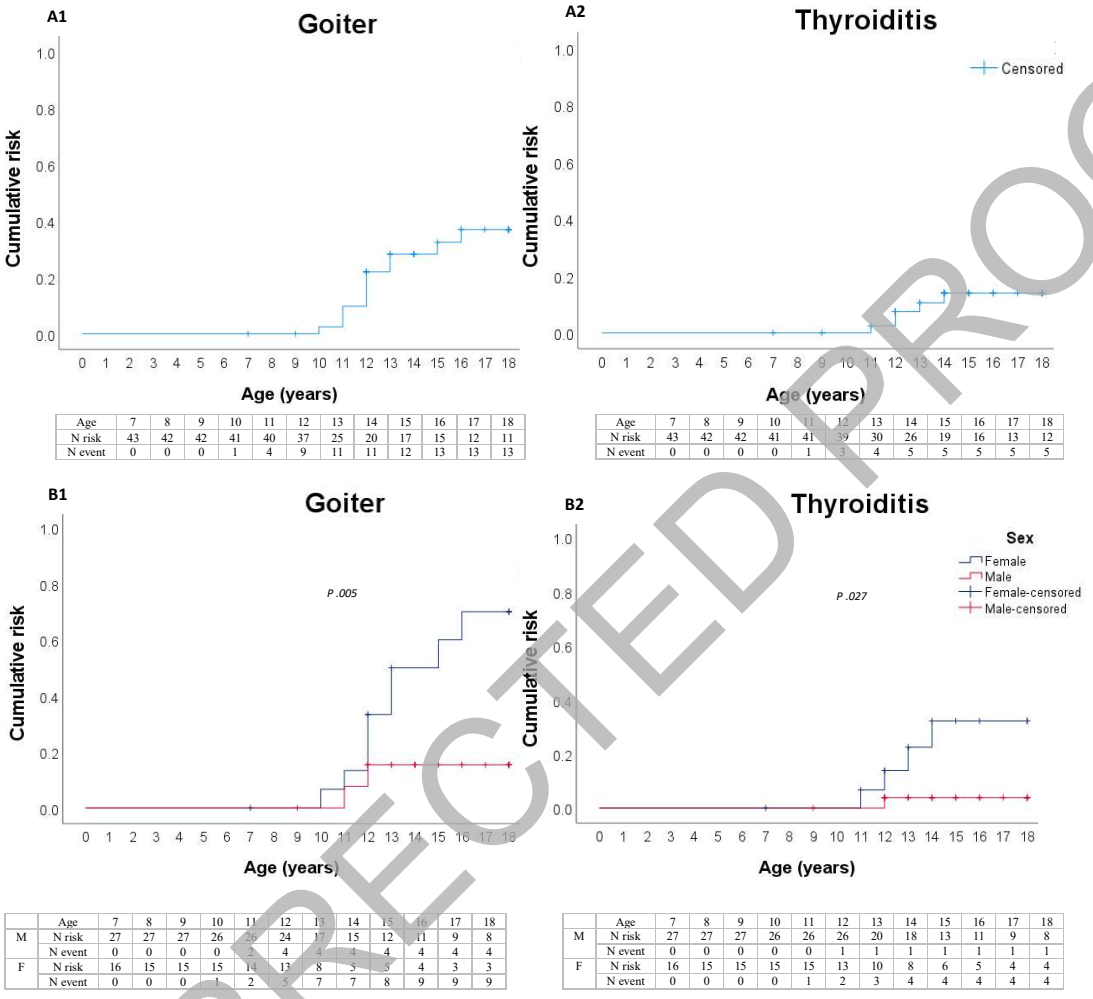
	Age	7	8	9	10	11	12	13	14	15	16	17	18
M	N risk	27	27	27	26	24	23	15	14	11	7	5	4
	N event	0	0	0	2	3	7	7	7	10	12	12	12
F	N risk	16	15	15	15	15	13	8	6	3	2	2	2
	N event	0	0	0	0	2	5	6	8	9	9	9	9

	Age	7	8	9	10	11	12	13	14	15	16	17	18
M	N risk	27	27	27	26	26	25	20	18	11	9	8	6
	N event	0	0	0	0	1	1	1	3	4	4	5	5
F	N risk	16	15	15	15	15	14	11	8	4	4	3	3
	N event	0	0	0	0	1	2	4	7	7	7	7	9

Figure 2 – Cumulative risk of thyroid nodular disease. Time-to-event is presented for a nodule ≥10mm (1) and for nodular growth (2), for all patients (A), by head circumference SDS (B) and by sex (C) (M=male, F=female). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards. Log-rank tests P-values are provided.

Figure 3 – Cumulative risk of goiter and thyroiditis
Cumulative risk of goiter (1) and thyroiditis (2) on ultrasound. Time-to-event is presented for all patients (A) and by sex (B) (M=male, F=female). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards. Log-rank tests P-values are provided.

Figure 3 – Cumulative risk of goiter and thyroiditis



	Age	7	8	9	10	11	12	13	14	15	16	17	18
	N risk	43	42	42	41	40	37	25	20	17	15	12	11
	N event	0	0	0	1	4	9	11	11	12	13	13	13

	Age	7	8	9	10	11	12	13	14	15	16	17	18
	N risk	43	42	42	41	41	39	30	26	19	16	13	12
	N event	0	0	0	0	1	3	4	5	5	5	5	5

	Age	7	8	9	10	11	12	13	14	15	16	17	18
M	N risk	27	27	27	26	26	24	17	15	12	11	9	8
	N event	0	0	0	0	2	4	4	4	4	4	4	4
F	N risk	16	15	15	15	14	13	8	5	5	4	3	3
	N event	0	0	0	1	2	5	7	7	8	9	9	9

	Age	7	8	9	10	11	12	13	14	15	16	17	18
M	N risk	27	27	27	26	26	26	20	18	13	11	9	8
	N event	0	0	0	0	0	1	1	1	1	1	1	1
F	N risk	16	15	15	15	15	13	10	8	6	5	4	4
	N event	0	0	0	0	1	2	3	4	4	4	4	4

Figure 3 – Cumulative risk of goiter (1) and thyroiditis (2) on ultrasound. Time-to-event is presented for all patients (A) and by sex (B) (M=male, F=female). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards. Log-rank tests P-values are provided.

Nodule ≥10mm	***P-value***	**Goiter**	***P-value***

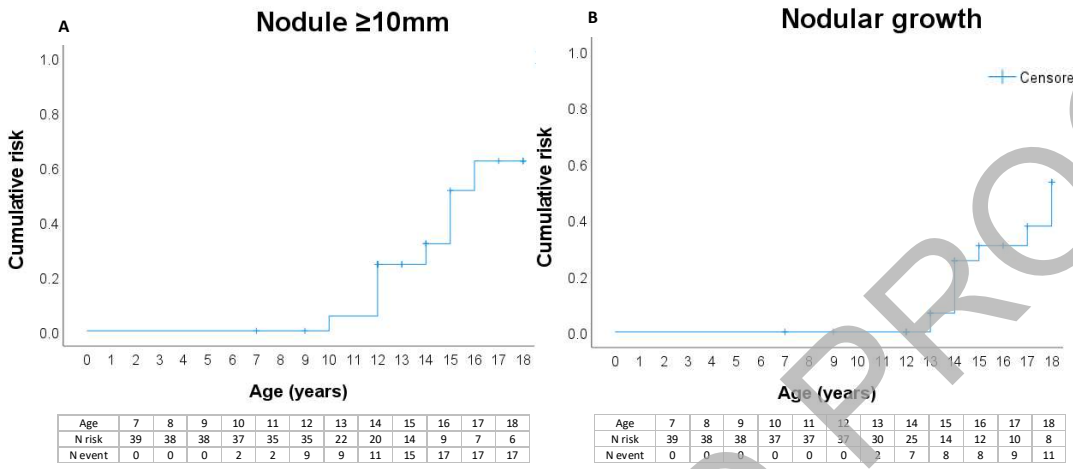
Characteristics		*Characteristics*	
Sex	0.237	Sex	**0.005**
Head circumference ≤4.0 / >4.0	**0.006**	Head circumference ≤4.0 / >4.0	0.140
Presence of lipomas	0.336	Presence of lipomas	0.242
Developmental delay	0.276	Developmental delay	0.651
Family history thyroid disease	0.116	Family history thyroid disease	0.277
Nodular growth	*P-value*	**Thyroiditis**	*P-value*
Characteristics		*Characteristics*	
Sex	**0.008**	Sex	**0.027**
Head circumference ≤4.0 / >4.0	0.182	Head circumference ≤4.0 / >4.0	0.506
Presence of lipomas	0.573	Presence of lipomas	0.718
Developmental delay	0.753	Developmental delay	0.196
Family history thyroid disease	0.723	Family history thyroid disease	0.613

Table 3 – Log-rank tests for associations with thyroid abnormalities

For each outcome (nodule≥10mm, nodular growth, goiter and thyroiditis), different clinical characteristics have been analyzed to test if there was an association. Every clinical characteristic was divided in 2 subgroups before performing a log-rank test, namely:
1. Female sex / male sex
2. Head circumference ≤4.0 / >4.0
3. Presence of lipomas yes / no
4. Developmental delay as presenting feature yes / no
5. Having a family member with thyroid disease yes / no

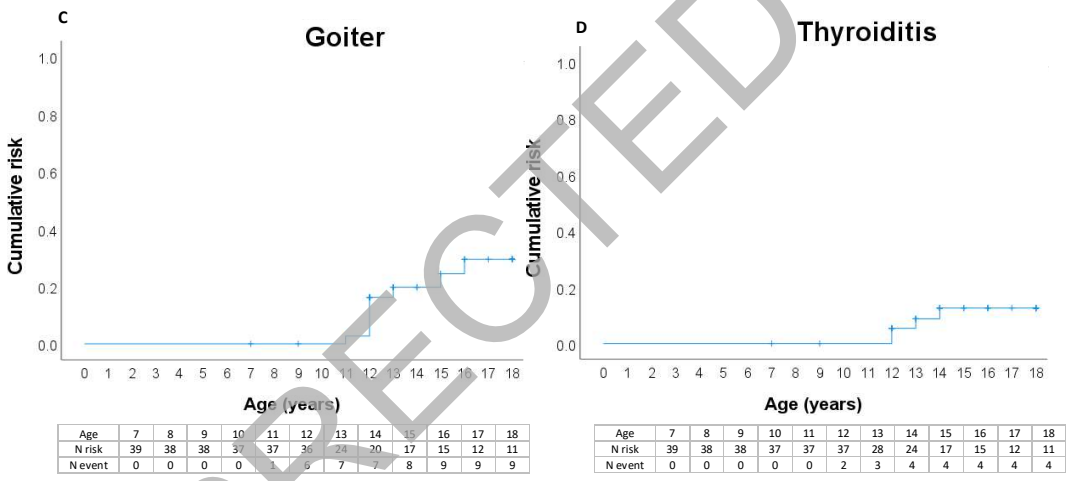
Supplementary Figure S1 – Kaplan-Meier Analyses without 4 index patients
Cumulative risk of a nodule ≥10mm (A), nodular growth (B), goiter (C) and thyroiditis (D). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards.

Supplementary Figure S1 – Kaplan-Meier Analyses without 4 index patients



Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	39	38	38	37	35	35	22	20	14	9	7	6
N event	0	0	0	2	2	9	9	11	15	17	17	17

Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	39	38	38	37	37	37	30	25	14	12	10	8
N event	0	0	0	0	0	0	2	7	8	8	9	11



Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	39	38	38	37	37	36	24	20	17	15	12	11
N event	0	0	0	0	1	6	7	7	8	9	9	9

Age	7	8	9	10	11	12	13	14	15	16	17	18
N risk	39	38	38	37	37	37	28	24	17	15	12	11
N event	0	0	0	0	0	2	3	4	4	4	4	4

Supplementary Figure S1 – Kaplan-Meier analyses without 4 index patients: Cumulative risk of a nodule ≥10mm (A), nodular growth (B), goiter (C) and thyroiditis (D). The number of patients at risk (N Risk) and the cumulative number of events (N Event) are presented for each age category from age 7 years onwards.